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EVALUATION OF HYDROCORTISONE, VITAMIN C, AND THIAMINE FOR THE TREATMENT OF SEPTIC SHOCK: A RANDOMIZED CONTROLLED TRIAL (THE HYVITS TRIAL)

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ABSTRACT—**Purpose:** The aim of the study is to evaluate the effect of combined hydrocortisone, vitamin C, and thiamine (triple therapy) on the mortality of patients with septic shock. **Methods**: This multicenter, open-label, two-arm parallel-group, randomized controlled trial was conducted in four intensive care units in Qatar. Adult patients diagnosed with septic shock requiring norepinephrine at a rate of ≥0.1 μg/kg/min for ≥6 h were randomized to a triple therapy group or a control group. The primary outcome was in-hospital mortality at 60 days or at discharge, whichever occurred first. Secondary outcomes included time to death, change in Sequential Organ Failure Assessment (SOFA) score at 72 h of randomization, intensive care unit length of stay, hospital length of stay, and vasopressor duration. **Results:** A total of 106 patients (53 in each group) were enrolled in this study. The study was terminated early because of a lack of funding. The median baseline SOFA score was 10 (interquartile range, 8–12). The primary outcomes were similar between the two groups (triple therapy, 28.3% *vs.* control, 35.8%; $P = 0.41$). Vasopressor duration among the survivors was similar between the two groups (triple therapy, 50 h *vs.* control, 58 h; $P = 0.44$). Other secondary and safety endpoints were similar between the two groups. **Conclusion:** Triple therapy did not improve in-hospital mortality at 60 days in critically ill patients with septic shock or reduce the vasopressor duration or SOFA score at 72 h. **Trial Registration:** ClinicalTrials.gov identifier: NCT03380507. Registered on December 21, 2017.

KEYWORDS—Ascorbic acid; hydrocortisone; septic shock; thiamine; vitamin C

BACKGROUND

Despite recent medical advances, sepsis and septic shock remain major causes of death (1,2). Approximately 20% of deaths worldwide are associated with sepsis (2). In addition, mortality from septic shock is approximately 30%–40% as reported in a recent meta-analysis of 71 studies (3). There is an ongoing effort to identify novel therapies or repurposed medications to improve outcomes in patients with sepsis and septic shock.

Low plasma levels of ascorbic acid (vitamin C) have been associated with multiorgan dysfunction in critically ill patients (4–6). Several studies have demonstrated the safety and benefits of using vitamin C to treat critically ill patients, including a dose-dependent decrease in the Sequential Organ Failure Assessment (SOFA) score, lower vasopressor doses and duration, and lower fluid resuscitation requirements (7–10).

A small study demonstrated that septic shock is associated with thiamine deficiency (11). Donnino et al. showed that intravenous thiamine decreased lactate levels and mortality in a subgroup of patients with thiamine deficiency, but this finding was not observed in the entire study population (12). In an *in vitro* study, a combination of hydrocortisone and vitamin C preserved

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AM, A Shible, A-RA, MA, and ML were staff at Hamad Medical Corporation during the study conception and design and during part or all the study recruitment period.

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The combination of hydrocortisone, vitamin C, and thiamine is not labeled for use in septic shock.

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the endothelial integrity of the lung vascular endothelial cells exposed to endotoxins (13). Another retrospective study suggested that a combination of hydrocortisone, vitamin C, and thiamine may decrease the mortality rate in sepsis (14).

This study aimed to examine the effect of combined hydrocortisone, vitamin C, and thiamine on in-hospital mortality at 60 days in critically ill patients with septic shock.

METHODS

Design and settings

This study was a multicenter, randomized, open-label, two-arm parallel-group, pragmatic trial comparing a combination of hydrocortisone, vitamin C, and thiamine plus standard care with standard care alone in patients with septic shock. This study was performed in accordance with the Declaration of Helsinki and was approved by the Hamad Medical Corporation Institutional Review Board (17207/17) and the Ministry of Public Health in Qatar. The trial was monitored by an independent data safety monitoring board (DSMB), which reviewed and approved the protocol before patient enrollment.

This study evaluated patients admitted to two medical and two surgical intensive care units in two government hospitals within the Hamad Medical Corporation (HMC) health system in Qatar between March 2018 and August 2019.

Population

Adult patients older than 18 years with suspected or documented infection who met the criteria for septic shock requiring norepinephrine at a dose of more than or equal to 0.1 μg/kg/min were screened for inclusion. The diagnosis of septic shock was based on persistent hypotension requiring vasopressor therapy to maintain a MAP of more than or equal to 65 mm Hg and having a serum lactate level of more than 2 mmol/L, despite adequate volume resuscitation. Patients were excluded if they were pregnant or had acute cerebral vascular events, acute coronary syndrome, status asthmaticus, a significant cardiac arrhythmia, active gastrointestinal bleeding, active seizures, drug overdose, an acute burn, acute trauma, requirement for immediate surgery, an absolute neutrophil count of less than 500 mm^3, a CD4 count of less than 50/mm^3, a do-not-resuscitate status, advanced directives restricting implementation of the protocol, a terminally ill status in palliative care, participation in another interventional study, a known allergy, or a contraindication to one or more of the trial medications. Patients with septic shock who required immediate surgery were evaluated postoperatively for inclusion in the study.

Outcomes

The primary outcome was hospital mortality evaluated at hospital discharge or at 60 days, whichever came first. Secondary outcomes included time to death, clinical evidence of organ dysfunction (SOFA scores at 72 h), intensive care unit (ICU) length of stay (LOS), hospital LOS, duration of vasopressor therapy, need for renal replacement therapy for acute kidney injury, and need for extracorporeal membrane oxygenation. Safety outcomes included the incidence of nephrolithiasis, secondary infections, mechanical ventilator weaning failure, hypernatremia, hypokalemia, hemolysis, and gastrointestinal bleeding.

Consent, randomization, and enrollment

After screening the patients for eligibility, delegated investigators obtained consent from eligible patients or their legally authorized representatives to participate in the study.

Proxy consent signed by a legally authorized representative was obtained for any incapacitated patients. Once capacity was regained, informed consent was obtained from the patient to continue participation in the study. In the case of a patient declining to continue in the study, the collected data were eliminated, and the study intervention was stopped if the patient was in the treatment group. For incapacitated patients without legally authorized representatives available, deferred consent was obtained by two independent physicians who were not part of the study.

The enrolled subjects were randomized in a 1:1 ratio with stratification by study site *via* a web-based randomization system (https://randomizer.at). Permuted block randomization with variable block sizes was used for treatment allocation. The participants were enrolled and assigned a study identification number (ID#) and treatment allocation.

Study interventions

The treatment group received standard care according to the hospital's Adult Sepsis Care Pathway plus triple therapy, while the control group received standard care only.

The triple therapy regimen consisted of intravenous vitamin C (1.5 gm q 6 hourly for 4 days or until ICU discharge, whichever was earlier), hydrocortisone (50 mg q 6 hourly for 7 days or until ICU discharge, whichever was earlier, followed by a taper over 3 days), and intravenous thiamine (200 mg q 12 hourly for 4 days or until ICU discharge, whichever was earlier). Vitamin C was administered over 30–60 min as an infusion mixed in a 100-mL solution of either dextrose 5% in water (D5W) or normal saline. Intravenous thiamine and hydrocortisone were administered as 30-min infusions in 50 mL of either D5W or normal saline.

Modification of the triple therapy intervention was not permitted. However, discontinuation of the treatment intervention was possible if a recruited patient requested to withdraw from the study after randomization to the treatment arm or if the patient developed an adverse drug reaction that was deemed to be a direct result of one or more components of the triple therapy intervention. Otherwise, patients randomized to the treatment arm completed the treatment duration, regardless of clinical progression. The primary care team continued to provide all other aspects of care to the patients (e.g., admission, physical examinations, interventions, and consultations).

Data safety monitoring board

All DSMB members were approved by the hospital's medical research center, the hospital's institutional review board, and the Ministry of Public Health in Qatar. All the members were appointed before trial initiation.

The DSMB was responsible for monitoring efficacy and safety. The DSMB provided an independent review of the study design and ethical and scientific conduct of the study. Based on this review, the DSMB submitted recommendations to the study investigators; these recommendations included, but were not limited to, continuation, modification, or termination of the study.

Statistical analysis

Marik et al. demonstrated a reduction in mortality from 40.4% in the control group to 8.5% in the treatment group, representing a relative risk reduction (RRR) of approximately 79% (14). However, because of concerns about an overestimated effect size in the aforementioned study, a more conservative estimate of RRR (50%) was used for sample size determination.

We estimated that 188 patients would provide a power of more than 80% to detect an RRR of approximately 50% in the primary outcome between the two arms, assuming that the mortality in the control arm would be approximately 40% (based on institutional data and mortality rate in the control group of the study by Marik et al.) using a two-sided test at a significance level of 0.05 (14).

Therefore, we planned to enroll 212 patients (106 in each group) to account for 10% of anticipated withdrawals.

Regarding the primary outcome, the number and percentage of hospital mortalities after randomization were reported for each treatment group, and a logistic regression model was used to account for baseline Acute Physiology and Chronic Health Evaluation (APACHE) II score and randomization site. Analysis was performed according to the intention-to-treat principle.

Secondary binary outcomes (e.g., renal replacement therapy) were compared using the chi-square test. Secondary numeric outcomes (e.g., SOFA score, ICU LOS, and hospital LOS) were compared using the Wilcoxon rank sum test. The maximum possible SOFA score (24 points) was used for patients who died within 72 h of initiation of triple therapy. Time to death was evaluated using the Kaplan-Meier method. Statistical analyses were performed using Stata statistical software (release 16).

RESULTS

Enrollment and baseline characteristics

A total of 173 patients were screened between March 2018 and August 2019 (Fig. 1), and 106 patients were recruited and included in the final analysis (53 patients per group). Recruitment was paused because of the COVID-19 pandemic. The study was terminated early because of a lack of funding and probable futility after other larger trials were already published and showed no benefit of triple therapy on outcomes in sepsis and septic shock.

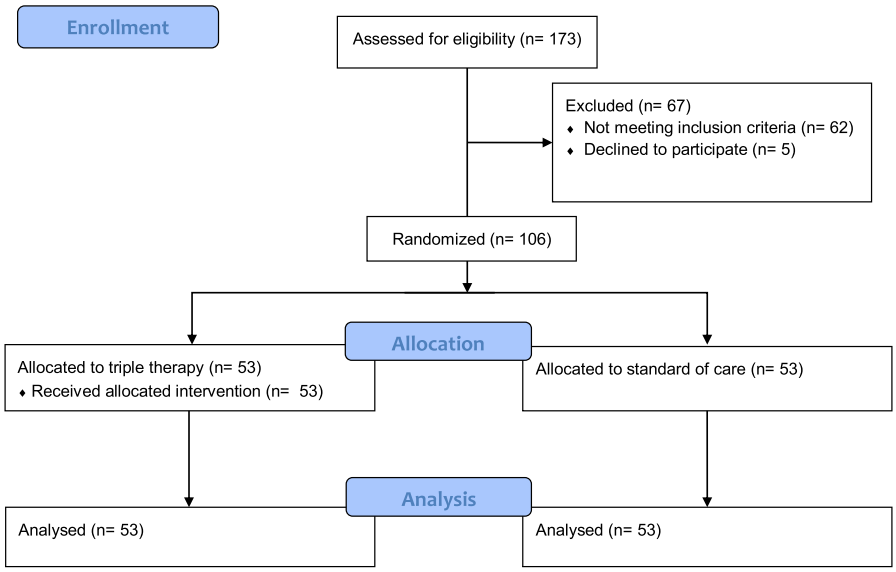

FIG. 1. **Consolidated Standards of Reporting Trials (CONSORT) 2010 flow diagram**.

The mean age was 49.2 years, and the majority of patients were male (70.8%). The median baseline SOFA score was 10 (interquartile range [IQR], 8–12), and the median baseline APACHE II score was 25 (IQR, 20–30). Two thirds of the patients were admitted to medical ICUs. The most common sources of infection were pulmonary (35.8%), intra-abdominal (27.4%), and genitourinary (17.9%). All patients in the intervention group received a stress dose of hydrocortisone, as per study protocol, and 67.9% of patients in the control group received a stress dose of hydrocortisone. The median lactate level at randomization was 4.8 mmol/L, and 59.4% of patients received invasive mechanical ventilation at randomization.

The baseline characteristics and illness severity scores (SOFA and APACHE II) were similar between the two groups. There were more male patients and less patients with malignancy in the triple therapy group. Table 1 and Supplementary Table 1, http://links.lww.com/SHK/B649, provide the baseline and clinical characteristics of the enrolled patients.

Primary outcome

No statistically significant difference was determined in hospital mortality at 60 days or at discharge between the triple therapy and control groups (28.3% *vs.* 35.8%, respectively, $P = 0.41$). There was also no statistically significant difference after accounting for the baseline APACHE II score and randomization site (odds ratio = 0.69; 95% confidence interval = 0.29–1.64, $P = 0.40$). Table 2 presents the full details of the outcomes.

Key secondary endpoints

No statistically significant difference was found between the triple therapy and control groups in the duration of vasopressor therapy among survivors (50 h [IQR, 22–91 days] *vs.* 58 h [IQR, 31.4–82.8 days]). The duration of mechanical ventilation was also similar between the two groups of survivors. The change in SOFA score at 72 h was similar between the two groups ($P = 0.54$). The need for renal replacement therapy was similar between the two groups (triple therapy, 41.2% *vs.* control, 41.7%; $P = 0.96$). Kaplan-Meier survival analysis for time to death is shown in Figure 2.

TABLE 1. **Baseline characteristics of patients**

Patient characteristic	Control (n = 53)	Triple therapy (n = 53)
Age, mean (SD), y	49.1 (16.5)	49.2 (15.5)
Sex (male), n (%)	32 (60.4)	43 (81.1)
Weight, mean (SD), kg	73.2 (22.8)	71.7 (21.4)
Comorbidities, n (%)		
Hypertension	21 (39.6)	19 (35.8)
Diabetes mellitus	22 (41.5)	16 (30.2)
Chronic kidney disease	13 (24.5)	10 (18.9)
Chronic liver disease	7 (13.2)	7 (13.2)
Chronic pulmonary disease	1 (1.9)	5 (9.4)
Cancer	10 (18.9)	2 (3.8)
Immunosuppressant medications, n (%)	6 (11.3)	8 (15.1)
Postoperative randomization, n (%)	13 (24.5)	11 (20.8)
Study ICU, n (%)		
Medical	36 (67.9)	38 (71.7)
Surgical	17 (32.1)	15 (28.3)
Admitting diagnosis, n (%)		
Sepsis	9 (17)	2 (3.8)
Septic shock	43 (81.1)	51 (96.2)
Other	1 (1.9)	0
Source of infection, n (%)		
Pulmonary	15 (28.3)	23 (43.4)
Intra-abdominal	16 (30.2)	13 (24.5)
Urinary	8 (15.1)	11 (20.8)
Skin and soft tissue	7 (13.2)	5 (9.4)
Central nervous system	2 (3.8)	0
Catheter-related	3 (5.7)	0
Unknown origin	2 (3.8)	1 (1.9)
Mechanical ventilation at randomization, n (%)	32 (60.4)	31 (58.5)
Serum creatinine, mean (SD), mg/dL	182.4 (146.8)	177.3 (151.8)
APACHE II score, mean (SD)	25 (7)	25 (7)
SOFA score, median (IQR)	10 (8–13)	10 (8–12)
Serum lactate, median (IQR), mmol/L	4.8 (2.9–8)	4.9 (3–8)

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

TABLE 2. **Clinical efficacy outcomes**

Outcome	Control (n = 53)	Triple therapy (n = 53)	*P*
Primary endpoint			
Hospital mortality at 60 d, n (%)*	19 (35.8)	15 (28.3)	0.40
Secondary endpoints			
ICU LOS, median (IQR),† d	9.5 (5 to 15)	9.5 (5 to 14)	0.83
Hospital LOS, median (IQR)†	22 (9–48)	18.5 (12–36)	0.88
Duration of vasopressor therapy, median (IQR),† h	58.1 (31.4 to 82.8)	49.9 (21.8 to 91.2)	0.44
Duration of mechanical ventilation, median (IQR),† d	7.5 (4.5 to 11.5)	6 (3 to 10)	0.36
Need for RRT, n (%)‡	20/48 (41.7)	21/51 (41.2)	0.96
SOFA score at 72 h, median (IQR)	10 (7 to 16)	8 (6 to 12)	0.16
Change in SOFA score at 72 h, median (IQR)	–1 (–4 to 3)	–2 (–4 to 1)	0.54

ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment.
*Mortality was calculated at hospital discharge or 60 days, whichever came first.
†Length of stay, duration of vasopressor therapy, and duration of mechanical ventilation were calculated for survivors only.
‡ Patients on RRT before randomization were excluded.

Safety outcomes

No difference was found in the safety outcomes between the two groups (Supplementary Table 2, http://links.lww.com/SHK/B649). Although more mechanical ventilation weaning failures were noted in the triple therapy group (80% *vs.* 64.1%), the difference was not statistically significant ($P = 0.12$).

DISCUSSION

In this open-label randomized controlled trial, the combination of hydrocortisone, vitamin C, and thiamine did not decrease the in-hospital mortality at 60 days or at discharge in patients with septic shock. The triple-drug combination did not shorten the duration of vasopressor therapy or mechanical ventilation and did not improve the SOFA score at 72 h.

This study had similar results to previous randomized controlled trials evaluating the use of hydrocortisone, vitamin C, and thiamine in patients with sepsis and septic shock. The VITAMINS, ACTS, and VICTAS trials did not report a reduction in mortality (15–17). There was also no reduction in vasopressor duration in either the VITAMINS or the VICTAS trials (15,17).

The mean SOFA score at enrollment was higher in our study (10.4 ± 3.3) than those in similar studies (15–18). We enrolled patients requiring norepinephrine 0.1 μg/kg/min for more than or equal to 6 h, which may explain the higher SOFA score at enrollment. Similar to the VICTAS and ACTS trials, a combination of hydrocortisone, vitamin C, and thiamine did not reduce the SOFA score at 72 h (16,17).

The duration of vasopressor therapy was similar between the two groups and similar to the vasopressor duration reported in other multicenter randomized controlled trials (15,17). Recent meta-analyses suggested that high-dose intravenous vitamin C or a combination of hydrocortisone, vitamin C, and thiamine was associated with shorter duration of vasopressor therapy (19,20). The vasopressor therapy duration outcome in the meta-analysis by Sato et al. was heavily influenced by smaller single-center studies (19). In addition, the use of stress doses of steroids or hydrocortisone was not considered in the meta-analyses. There was significant heterogeneity among the included studies, which might have had a direct impact on the duration of vasopressor therapy and shock resolution (19). In our study, 67.9% of the patients in the control group received steroids. Unlike the meta-analysis by Sato et al., the

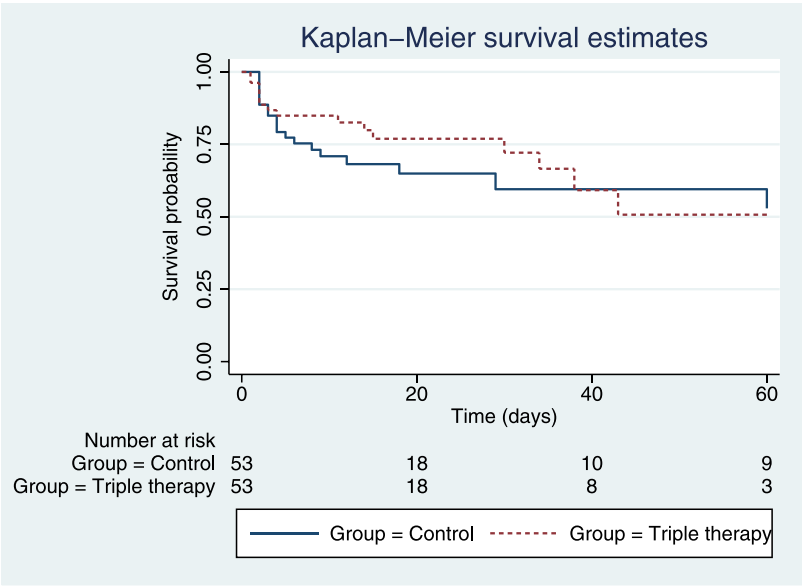

FIG. 2. **Kaplan-Meier survival analysis.** The log-rank test for survival time between the two groups is not statistically significant ($P = 0.44$).

meta-analysis by Assouline et al. did not include the VICTAS trial in their vasopressor therapy duration analysis (19,20).

The ORANGES trial showed a significant decrease in the duration of vasopressor therapy with combination therapy; however, the study had several limitations that may have overestimated the treatment effect (18). Only 43.8% of patients who were on vasopressors in the control arm received corticosteroids. In addition, the primary outcome was changed from hospital mortality to time to vasopressor independence and change in SOFA score after the end of patient enrollment (study enrollment period between February 14, 2018, and April 29, 2019). This change in the primary outcome after the study conclusion may have introduced a significant bias into the study. While the difference in the duration of vasopressor therapy between the two groups was 26 h, this reduction did not affect the SOFA score, ICU LOS, or hospital LOS (18).

The LOVIT trial, a randomized controlled trial, evaluated the use of high-dose vitamin C (50 mg/kg) in patients with sepsis (21). The primary outcome was composite death or persistent organ dysfunction. In total, 863 patients were included in the primary outcome analysis. The incidence of primary composite outcomes was significantly higher in the vitamin C group than in the placebo group (21). In a meta-analysis by Agrawal et al., the use of vitamin C did not improve survival, and there was a signal of increased harm in the subgroup analysis of low risk of bias and moderate-certainty studies (22). Therefore, the totality of evidence shows no mortality or clinical benefit with the use of vitamin C alone or in combination with thiamine and hydrocortisone, and there may be an increased risk of harm. The findings of this study, along with the other published evidence, support the current surviving sepsis guideline recommendation against the use of the triple therapy (15–18,21,23).

This study had several limitations. First, the open-label design may have introduced bias. Second, we did not initiate the triple therapy combination in the first few hours of shock. We only included patients with septic shock who had been on norepinephrine 0.1 μg/kg/min for 6 h or more. Lastly, the planned sample size and statistical power were not achieved because the trial was terminated prematurely because of a lack of funding.

CONCLUSIONS

A combination of hydrocortisone, vitamin C, and thiamine did not improve in-hospital mortality at 60 days in patients with septic shock requiring vasopressor support, nor did it reduce the duration of vasopressor therapy or SOFA scores at 72 h. The trial may have been insufficiently powered because of premature termination. However, previously published studies support the lack of benefits of this triple therapy in patients with septic shock.

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